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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,845	01/17/2006	Tatsuo Hoshino	21419 US C038435/0185660	2036
7590 Stephen M Haracz Bryan Cave 1290 Avenue of the Americas New York, NY 10104-3300			EXAMINER CHOWDHURY, IQBAL HOSSAIN	
			ART UNIT	PAPER NUMBER
			1652	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No. 10/528,845	Applicant(s) HOSHINO ET AL.	
	Examiner Iqbal H. Chowdhury, Ph.D.	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 November 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 is/are pending in the application.
- 4a) Of the above claim(s) 3, 8, 12 and 13 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 4-7, 9 and 10 is/are rejected.
- 7) ☒ Claim(s) 11 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>03/05</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This application is a 371 of PCT/EP00/10575.

The preliminary amendment filed on 3/23/2005 amending claims 9-10 and adding new claims 11-13 is acknowledged.

Claims 1-13 are currently pending in the instant application.

Election/Restriction

Applicant's election with traverse of Group I, Claims 1-2, 4-6, 7, 9-10 and 11, drawn to an isolated polynucleotide encoding a polypeptide vitamin B6 phosphate phosphatase, vector and recombinant microorganism comprising said gene in the response filed on 11/27/2006 is acknowledged.

The traversal is on the ground(s) that the restriction requirement based on PCT Rule 13.1 and PCT Rule 13.2, of Group I (drawn to an isolated polynucleotide encoding a polypeptide), Group II (drawn to isolated polypeptide) and Group III (drawn to a process for producing vitamin B6 by using said polypeptide) is not proper.

Examiner, in his previous Office action, clearly showed that the polynucleotide of Group I and polypeptide of Group II, each unrelated and chemically distinct entities. The only shared technical feature of these groups is that they all relate to polynucleotide encoding said polypeptide. However, this shared technical feature is not a "special technical feature" as defined by PCT Rule 13.2 as it does not define a contribution over the art. In the instant case Examiner

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has shown that the prior art already comprises a polynucleotide (GenBank Accession No. AL591783) encoding a vitamin B6 phosphate phosphatase having an amino acid sequence more than 70% sequence identity opposed to what is claimed in claim1 of the instant application. Thus, while the groups may share a special technical feature, the invention lacks unity of invention when it can be shown that invention does not contribute over what is already known in prior art. Examiner agrees with the law as applicants describe, but disagrees in applicant's interpretation of the special or corresponding special technical feature of Groups I-III.

Applicants also argue by showing an Exhibit that according to the IPER, there is no lack of unity. It is not clear to the Examiner as to why the lack of unity was not recognized during the examination of PCT application. However, examination at the national phase is not bound by the findings of PCT application.

Applicants further argue that there are deficiencies with the arguments made by the Examiner, i.e. the Examiner fails to identify where in AL591783 it is disclosed that the translation product defined by the polynucleotide sequence encodes "a vitamin B6 phosphate phosphatase". Examiner disagrees and takes the position that the reference provides the encoded amino acid sequence whose inherent property is phosphatase activity

The requirement is still deemed proper and is therefore made **FINAL**.

Claims 3, 8 and 12-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-2, 4-7, 9-11 are currently under consideration and will be examined.

Priority

Acknowledgement is made of applicants claim for priority of foreign application EPO 02021622.2 filed on 9/27/2002.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 3/23/2005 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

The drawing of this application submitted on 3/23/2005 is being considered by the examiner.

Claim Objections

Claim 1 part (a), (c), (d) is objected to with the recitation "sequence represented in", Examiner suggests amending the phrase to recite "sequence of". Appropriate correction is required.

Claim 1 part (b), (c), (d) is objected to with the recitation "sequence which encodes", Examiner suggests amending the phrase to recite, "sequence encoding". Appropriate correction is required.

Claim 1 part (b), is objected to with the recitation "fragment of thereof", Examiner suggests amending the phrase to recite, "fragment thereof". Appropriate correction is required.

Claim Rejections - 35 USC § 112 (Deposit requirement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-6 and 9-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ novel microorganisms (S. meliloti IFO14782/pVKPtacpdxP and E. coli JM109/pKKpdxP) comprising a gene encoding vitamin B6 phosphate phosphatase. Since the microorganisms are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The recited microorganisms have not been shown to be publicly known and freely available. The enablement requirements of 35 § U.S.C. 112 may be satisfied by a deposit of the microorganisms. The specification does not disclose a repeatable process to obtain the microorganisms and it is not apparent if the microorganisms are readily available to the public. Accordingly, it is deemed that a deposit of these microorganisms should have been made in accordance with 37 CFR 1.801-1.809.

If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty

and that the strain will be available to the public under the conditions specified in 37 CFR 1.808, would satisfy the deposit requirement made herein.

If the deposit is not made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

1. during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
2. upon granting of the patent the strain will be available to the public under the conditions specified in 37 CFR 1.808;
3. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and
4. the deposit will be replaced if it should ever become unavailable.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-2 and 4-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the phrase "hybridizes under standard conditions". However, the specification does not define what conditions constitute "standard conditions" for hybridization. While page 3 attempts to describe "standard conditions" for

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hybridization, the description is merely exemplary and not a clear definition. In the art the meaning of the term "standard" hybridizing conditions varies widely depending on the individual situation and the person making the determination. Therefore, it is not clear to the Examiner as to what hybridization conditions are encompassed in the above phrase. Accordingly, claims 2 and 4-7 are rejected as they depend on claim 1.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 and 4-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated DNA with SEQ ID NO: 9, which encodes a polypeptide vitamin B6 phosphate phosphatase enzyme of SEQ ID NO: 10 isolated from *S. meliloti*, does not reasonably provide enablement for any DNA that is 70% identical to SEQ ID NO: 9 or any DNA encoding a protein having phosphatase activity and having at least 70% identity to SEQ ID NO: 10 or any fragments thereof or any DNA which hybridizes under any standard conditions including low stringency conditions to SEQ ID NO: 9 and encodes a polypeptide having phosphatase activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731,737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows:

(1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence and absence of working examples, (4) the nature of the invention, (5)

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the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims. The factors, which have, lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed below:

The breath of the claims:

Claim 1 is so broad as to encompass any DNA that is 70% identical to SEQ ID NO: 9 or any DNA encoding a protein having at least 70% identity to SEQ ID NO: 10 or any fragments thereof or any DNA which hybridizes under any standard conditions including low stringency conditions to SEQ ID NO: 9. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of DNAs encoding proteins including mutants, variants and recombinants broadly encompassed by the claims. In the instant case the disclosure is limited to the nucleotide (SEQ ID NO: 9) and encoded amino acid sequence of only a single protein of SEQ ID NO: 10.

The amount of direction or guidance presented and the existence of working examples:

The specification does not support the broad scope of the claims which encompass any DNA that is 70% identical to SEQ ID NO: 9 or any DNA encoding a protein having at least 70% identity to SEQ ID NO: 10 or any fragments thereof because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting vitamin B6 phosphate phosphatase enzymatic activity and; (B) the general tolerance of vitamin B6 phosphate phosphatase polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any vitamin B6 phosphate phosphatase amino acid residues with an expectation of obtaining the desired biological function; and (D) the

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specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art:

The amino acid sequence of a protein encoded by a polynucleotide determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. In the instant case, the polynucleotide that is 70% identical to SEQ ID NO: 9 or the DNA encoding a polypeptide that is 70% identical to SEQ ID NO: comprises mutants, variants and recombinants. The art clearly teaches the high level of unpredictability with regard to the effect of structural changes in a protein's activity encoded by a polynucleotide sequence when no guidance/knowledge as to which amino acids in the encoded protein are required for activity has been provided. While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within encoded protein's sequence where amino acid modifications can be made (i.e. corresponding nucleotide changes in the DNA) with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. Whisstock et al. (2003) teach that prediction of protein function from sequence and structure is a difficult problem because homologous proteins often have

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different functions (see abstract). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple point mutations or substitutions. Similarly, at the time of the invention, there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing de novo stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (1999) and Seffernick et al. (2001), where it is shown that even small amino acid changes result in enzymatic activity changes.

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, and the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the

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basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102 (b) as being anticipated by Capela et al. (GenBank Accession No. AL591783 for nucleic acid, created 8/1/2001 see IDS, and GenBank Accession No. Q92SG4, for protein, created 12/1/2001). Instant claim drawn to a DNA/gene encoding any vitamin B6 phosphate phosphatase having at least 70% identity to SEQ ID NO: 10 or any fragments thereof or a DNA/gene which hybridizes under any standard conditions including low stringency conditions to SEQ ID NO: 9.

Capela et al. teach a DNA, which encodes a putative oxidoreductase type protein, is 99.5% identical to SEQ ID NO: 9 of the instant application, inherently a vitamin B6 phosphate phosphatase protein. Since, the broadest reasonable interpretation of claim 1 is any DNA sequence would hybridize at low stringency hybridizing conditions (Examiner interprets standard hybridizing condition as low stringency hybridizing condition) to SEQ ID NO: 9. Therefore, Capela et al. anticipates claim 1 of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

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1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 4, 7 and 11 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Capela et al. (GenBank Accession No. AL591783 for nucleic acid, created 8/1/2001 see IDS, and GenBank Accession No. Q92SG4, for protein, created 12/1/2001) and Jang et al. (Human pyridoxal phosphatase. Molecular cloning, functional expression, and tissue distribution, J Biol Chem. 2003 Dec 12; 278(50): 50040-6. Epub 2003 Sep 30). Instant claims are drawn to a DNA encoding vitamin B6 phosphate phosphatase or pyridoxal phosphatase having at least 70% identity to SEQ ID NO: 9 encoding a protein having at least 70% identity to SEQ ID NO: 10 or any fragments thereof, a vector comprising said DNA sequence, a host cell of E. coli, a process for preparing cell extract from transformed host cell.

Capela et al. teach a DNA, which encodes a putative oxidoreductase type protein, is 99.5% identical to SEQ ID NO: 9 of the instant application, inherently a vitamin B6 phosphate phosphatase protein. Capela et al. do not teach a vector comprising said sequence, transformed host cell and a method of producing said protein in transformed host cell and extraction of cell lysate.

However, Jang et al. teach human pyridoxal phosphatase or vitamin B6 phosphate phosphatase, its molecular cloning in a vector, functional expression in E. coli host cell, and process for producing said protein followed by extraction and purification (p50041, col1).

It would have been obvious to one of ordinary skill in the art at the time of the invention was made to combine the teachings of Capela et al. and Jang et al. to clone the DNA of Capela et al. in a vector, transform an E. coli host cell, a process for producing said protein in E. coli cells, extract the cell lysate and purification by using the teaching of Jang et al.

One of ordinary skill in the art would have been motivated for cloning the DNA of Capela et al. in a vector, transform an E. coli host cell, a process for producing the protein in said E. coli cell, extract the cell lysate by using the teaching of Jang et al for producing vitamin B6 by using S. meliloti derive phosphatase, since vitamin B6 is widely used in medicine and food additives.

One of ordinary skill in the art would have a reasonable expectation of success because cloning a gene, expression and a process for producing said protein is widely known and used in the art for over-producing interested protein in bacterial system.

Conclusion

Status of the claims:

Claims 1-13 are pending.

Claims 3, 8 and 12-13 are withdrawn.

Claims 1-2, 4-7 and 9-10 are rejected.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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